MEDICAL POLICY AND PROGRAM REVIEW COUNCIL
October 3, 2018, 9:00 AM, WO-Bldg. 22, Room 1315

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Purpose: Follow up discussion of Tracked Safety Issue 1355 for acetaminophen and effects during pregnancy

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AGENDA

I.	Presentation	15 minutes
II.	Discussion	45 minutes

BACKGROUND

Acetaminophen and its neurodevelopmental effects during pregnancy (TSI 1355) were discussed at the Medical Policy and Program Review Council (MPPRC) on January 24, 2018. At that time, the Division of Nonprescription Drugs (DNDP) explained that acetaminophen is a monograph drug (except for prescription intravenous acetaminophen and nonprescription acetaminophen extended-release products which are New Drug Applications (NDAs)) and lacks some of the current standard developmental and reproductive nonclinical toxicology study endpoints (e.g., functional assessments in the pre- and post-natal study, juvenile animal study).

Acetaminophen is the first-choice pain and fever reliever during pregnancy. As of January, eleven observational studies reported some association with adverse neurodevelopmental outcomes. A prior Drug Safety Communication (DSC) warns of risks associated with pain medicine use during pregnancy. Most observational studies had odds ratios in the range of 1.2-1.5; because of potential confounding factors (e.g., differences in substance abuse, alcohol use, concomitant medical illnesses that were more common in women taking acetaminophen), residual confounding cannot be ruled out even after adjustment, so it is not possible to confirm a causal association. Although more studies are likely in the future, the quality of the evidence is unlikely to change. DNDP sought guidance as to whether to release another communication, conduct a nonclinical study(ies), or to close the TSI.

Recommendations were as follows:

- The Council agreed with the Division and did not suggest making labeling changes.
- Given the uncertainty as to whether there is a causal association, issuing a communication at present would not add substantively to the prior DSC that counseled caution in use of any pain medication during pregnancy. It was suggested that a communication that generally reminded women to be cautious about the use of pain medication during pregnancy unless needed might be reasonable, without flagging specific concerns; however, such communication would need to be created hand-in-hand with the practicing community as well as with professional societies. A scholarly article comparing pain relievers could also be considered.
- The Division was to think about ways to obtain better clarity on the issues, whether through an Advisory Committee, workshop, or other venue.

- Most Council members did not support additional nonclinical studies if endpoints would be inadequate to inform further recommendations to the public. However, the diffuse range of potential clinical impacts may suggest a broader neurodevelopmental effect. It was therefore agreed that the team reach out to the National Center for Toxicological Research (NCTR) to discuss potential studies that might address this issue.
- The teams managing this TSI should return to MPPRC with a proposal for additional analyses or studies (observational clinical or nonclinical) that could shed additional light on this important issue.

As advised, the review team returns now to update the Council on related developments and seek advice on a potential nonclinical study.

NEW DEVELOPMENTS

TSI 1355: Acetaminophen and Effects During Pregnancy

There have been no new developments, (b) (5)

European Pharmacovigilance Issues Tracking Tool (EPITT) 12319: Paracetamol and Impact on the Urogenital Apparatus)

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Reference ID: 4337226

FDA's Division of Pediatric and Maternal Health (DPMH) reviewed the urogenital issue on February 9, 2010 and January 18, 2017 under prescription NDA 22-450 Ofirmev (intravenous acetaminophen). The Division of Anesthesia, Analgesia, & Addiction Products' (DAAAP's) Nonclinical team also noted the nonclinical literature suggesting an endocrine disruption effect of acetaminophen in rodents and noted these findings in their reviews. In 2010, the original NDA 22-450 Prescribing Information (PI) included the following description of the existing pre- and postnatal development study, which suggested the potential for adverse effects on testicular development in offspring:

- Section 8.1 Pregnancy - Data - Animal Data: *In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.*

- Section 13.1 Impairment of Fertility:
  In studies conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

  Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

When NDA 22-450's labeling was revisited during the review of a pediatric efficacy supplement in 2017, DAAAP Nonclinical noted additional published nonclinical findings, including reports suggesting that gestational exposure to acetaminophen is associated with a decrease in urogenital distance[1], suggesting a disruption in hormonally regulated sex differentiation. In 2017, the following information was added to the PI:

- Section 8.3 Females and Males of Reproductive Potential:
  Based on animal data use of acetaminophen may cause reduced fertility in males and females of

[1] Kristensen DM, Hass U, Lesne L, Lottrup G, Jacobsen PR, Desdoits-Lethimonier C, Boberg J, Petersen JH, Toppari J, Jensen TK, Brunak S, Skakkebaek NE, Nellemann C, Main KM, Jegou B and Leffers H (2011) Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. *Hum Reprod* **26**:235-244.

Kristensen DM, Lesne L, Le Fol V, Desdoits-Lethimonier C, Dejucq-Rainsford N, Leffers H and Jegou B (2012) Paracetamol (acetaminophen), aspirin (acetylsalicylic acid) and indomethacin are anti-androgenic in the rat foetal testis. *Int J Androl* **35**:377-384.

reproductive potential. It is not known whether these effects on fertility are reversible. Published animal studies reported that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, and reduced fertility. In female animals given the same doses, reduced implantation sites were reported. Additional published animal studies indicate that acetaminophen exposure in utero adversely impacts reproductive capacity of both male and female offspring at clinically relevant exposures [see Nonclinical Toxicology (13.1)].

- Section 13.1 Impairment of Fertility:
  In a published mouse study, oral administration of 50 mg/kg acetaminophen to pregnant mice from Gestation Day 7 to delivery (0.06 times the MHDD, based on a body surface area comparison) reduced the number of primordial follicles in female offspring and reduced the percentage of full term pregnancies and number of pups born to these females exposed to acetaminophen in utero.

  In a published study, oral administration of 350 mg/kg acetaminophen to pregnant rats (0.85 times the MHDD, based on a body surface area comparison) from Gestation Day 13 to 21 (dams) reduced the number of germ cells in the fetal ovary, decreased ovary weight, and reduced the number of pups per litter in F1 females as well as reduced ovary weights in F2 females.

The above labeling also includes results from studies, which suggest the potential for endocrine alterations in females as well as males. As noted earlier, decreased anogenital distance in males is believed to result from androgen deficiency during critical periods of male development which can lead to cryptorchidism, hypospadias, compromised fertility, and reduction in anogenital distance. Reference to the data suggesting decreased anogenital distance in animals was not specifically added to the labeling because the existing labeling already reflected adverse effects on testicular function during development and the term "anogenital distance" was not thought to be familiar to most prescribers.

Collectively, the nonclinical conclusions made by DAAAP are *consistent with the attached EMA PRAC report on acetaminophen-associated changes on the urogenital apparatus and clinical studies associating cryptorchidism, which are discussed below.*

Since FDA became of aware of EPITT 12319, the Division of Epidemiology (DEPI) identified the following studies in a recent literature search.

Study	**Data Source**	**Outcome**	**Risk estimate for prenatal acetaminophen exposure (versus unexposed except where indicated)**
Feldkamp 2010	National Birth Defects Prevention Study	Hypospadias	Adjusted OR 0.9 (0.7-1.1) for first trimester exposure overall; in subgroup of women with fever and infection, adjusted OR 0.42 (0.17-1.00)
Fisher 2016	Cambridge Baby Growth Study	Anogenital distance	Exposure during wks 8-14 associated with -0.27 SD reduction in anogenital distance (p=0.014). No association with exposure before or after wks 8-14
Interrante 2017	National Birth Defects Prevention Study	Hypospadias	Adjusted OR for NSAIDs vs acetaminophen = 1.3 (1.1-1.5). Acetaminophen vs. no exposure not analyzed

Jensen 2010	Danish National Birth Cohort	Cryptorchidism or orchiopexy	Exposure > 4 wks during wks 8–14: adjusted HR for cryptorchidism 1.38 (1.05–1.83), adjusted HR 1.44 (1.00-2.06) for orchiopexy
Kristensen 2010	Univ. Hosp. of Copenhagen	Cryptorchidism	Adjusted OR for cryptorchidism with acetaminophen use in 2nd trimester 1.97 (0.94–4.12). 2+ weeks acetaminophen use during first two trimesters significantly increased cryptorchidism prevalence, from ~ 7% to ~18% ($p<0.05$, OR not shown)
Lind 2017	Odense Child Cohort, Denmark	Anogenital distance, penile width	Penile width reduced 0.7 (0.3, 1.1) mm with exposure at "unknown time" during first 28 weeks, otherwise no statistically significant associations
Rebordosa 2008	Danish National Birth Cohort	Hypospadias and cryptorchidism	Hypospadias-- adjusted OR 1.01 (0.76-1.33) Cryptorchidism—adjusted OR 1.24 (0.79-1.94)
Snijder 2012	Generation R Study, the Netherlands	Hypospadias and cryptorchidism	For cryptorchidism, adjusted OR 1.89; 95% CI 1.01–3.51, with acetaminophen exposure in wk 14-22. No association w/hypospadias

- Some studies had negative findings, but that might have resulted from including exposure times of low relevance (i.e., early first trimester).
- The Feldkamp study found a reduction in the risk of hypospadias in the setting of fever and infection that almost reached statistical significance. A protective effect of antipyretics in the setting of maternal fever was also noted in some of the data on neurodevelopmental outcomes.

FDA will discuss the status of TSI 1355, EPITT 12319, and new TSI 1915 for acetaminophen and prenatal ductus arteriosus closure on October 24, 2018.

New TSI 1915: Acetaminophen and Prenatal Ductus Arteriosus Closure

In July, Becquet published an article which described two clinical cases of "certain" causality between maternal acetaminophen treatment and prenatal ductus arteriosus closure using the World Health Organization Uppsala Monitoring Center causality assessment system.[2] On September 12, 2018, the Office of Surveillance and Epidemiology's (OSE's) Division of Pharmacovigilance's (DPV's) completed its review of this issue, which identified 19 total cases in the literature (n=12) and FDA Adverse Event Reporting System (FAERS; n=7, including 2 literature cases). Due to the common use of acetaminophen in pregnant women, DPV concluded more data are needed to support this safety signal. DPMH's consult is pending.

Given the ~65% usage rate of OTC acetaminophen by women at some point during pregnancy[3], the six million pregnancies in the US each year, and the >60 years of acetaminophen marketing experience, one would expect a higher number of cases than those identified. Detailed clinical information is lacking in several of the above noted cases, such as missing data on timing and duration of drug exposure. It is not clear whether there are other

[2] Becquet O, et al. Paracetamol/acetaminophen during pregnancy induces prenatal ductus arteriosus closure. Pediatrics 2018;142(1):e20174021.
[3] M.M. Werler, A.A. Mitchell, S. Hernandez-Diaz, M.A. Honein, the National Birth Defects Prevention Study. Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol, 193 (2005), pp. 771-777.

unmeasured factors that contributed to these cases. Idiopathic prenatal closure/constriction of the ductus arteriosus does occur but is a rare event.[4]

Prenatal ductus arteriosus closure is commonly associated with NSAID use during the third trimester of pregnancy. NSAIDs reduce the production of prostaglandins by inhibition of the enzyme cyclooxygenase, whereas acetaminophen reduces the production of prostacyclin (PGI_2) through inhibition of the peroxidase site of prostaglandin synthase. Prostacyclin has vasodilatory and anti-aggregatory action, and its production normally increases during pregnancy. Acetaminophen's mechanism of action has led to current clinical research interest in the use of acetaminophen for closure of hemodynamically significant patent ductus arteriosus in premature, underweight neonates who have failed closure with the FDA-approved regimens with ibuprofen or indomethacin. The Clinical Trials.gov website reports 14 trials; three already completed (no results have been posted yet) and the remaining are recruiting, active, or of unknown status. When acetaminophen is used to induce closure of the ductus arteriosus in prematurely delivered infants, the common dose used is 15 mg/kg (oral, IV or gavage) administered every 6 hours for 3-15 days. It is not known if the *in utero* exposure to the fetus following maternal oral administration of acetaminophen is comparable to those exposures being administered to the premature neonate or sufficient to induce patent ductus arteriosus closure.

NCTR Nonclinical Protocol

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[redacted]

[4] Genovese F, Marilli I, Benintende G, Privitera A, Gulino FA, Iozza I, Cimino C, Palumbo MA Diagnosis and management of fetal ductus arteriosus constriction-closure..J Neonatal Perinatal Med. 2015 Mar 10.

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[redacted]

OPTIONS FOR DISCUSSION

- Conduct the proposed nonclinical study
  - Pros:

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  - Cons:

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- Do not conduct the proposed nonclinical study
  - Pros:

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  - Con:

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ATTACHMENTS

- MPPRC meeting minutes (January 24, 2018)
- Kristensen DM, Hass U, Lesne L, Lottrup G, Jacobsen PR, Desdoits-Lethimonier C, Boberg J, Petersen JH, Toppari J, Jensen TK, Brunak S, Skakkebaek NE, Nellemann C, Main KM, Jegou B and Leffers H (2011) Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. Hum Reprod 26:235-244.
- Kristensen DM, Lesne L, Le Fol V, Desdoits-Lethimonier C, Dejucq-Rainsford N, Leffers H and Jegou B (2012) Paracetamol (acetaminophen), aspirin (acetylsalicylic acid) and indomethacin are anti-androgenic in the rat foetal testis. Int J Androl 35:377-384.
- EMA PRAC signal assessment report about prenatal exposure to paracetamol and impact on urogenital apparatus or impact on neurodevelopment (February 8, 2018)
- Becquet O, et al. Paracetamol/acetaminophen during pregnancy induces prenatal ductus arteriosus closure. Pediatrics 2018;142(1):e20174021.
- OSE DPV Consult #2018-1282 for acetaminophen and prenatal ductus arteriosus closure (September 12, 2018)

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/s/

VALERIE S PRATT
10/18/2018

MPPRC – Acetaminophen and Pregnancy

October 3, 2018

Acetaminophen is the first-choice pain reliever and antipyretic during pregnancy. Acetaminophen and its neurodevelopmental effects during pregnancy were discussed at the MPPRC on January 24, 2018. At that time, the Division of Nonprescription Drugs (DNDP) explained that acetaminophen is a monograph drug and lacks some of the current standard developmental and reproductive nonclinical toxicology study endpoints.

Several observational studies were reviewed by the Council in January 2018. The studies had different neurodevelopmental endpoints and odds ratios in the range of 1.2 to 1.5 with concerns about potential confounding, including confounding by indication, as acetaminophen is used to treat fever and other co-morbidities that are also associated with the outcome. This led the Council to recommend that the team return to the MPPRC with a proposal for additional analyses or studies that could shed additional light on this important issue.

Since the last MPPRC meeting, the EMA informed FDA it is reviewing acetaminophen's impact on the urogenital apparatus, which is described to some extent in Ofirmev (intravenous acetaminophen) NDA 22-450's Prescribing Information. In July, Becquet published an article that describes two clinical cases of "certain" causality involving maternal acetaminophen treatment and prenatal ductus arteriosus closure, using the World Health Organization Uppsala Monitoring Center causality assessment system. OSE then identified 19 total cases in the literature (n=12) and FDA Adverse Event Reporting System (FAERS; n=7, including 2 literature cases). Because acetaminophen is commonly used in pregnant women, DPV concluded more data are needed to evaluate the ductus arteriosus safety signal.

It is biologically plausible that acetaminophen could lead to prenatal ductus arteriosus closure as acetaminophen reduces the production of prostacyclin (PGI2) through inhibition of the peroxidase site of prostaglandin synthase. It is being studied for intentional closure of patent ductus arteriosus in the post-natal setting.

The review team consulted the National Center for Toxicological Research (NCTR). NCTR's preliminary hypothesis is that (b) (5) .

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MPPRC – Acetaminophen and Pregnancy

October 3, 2018

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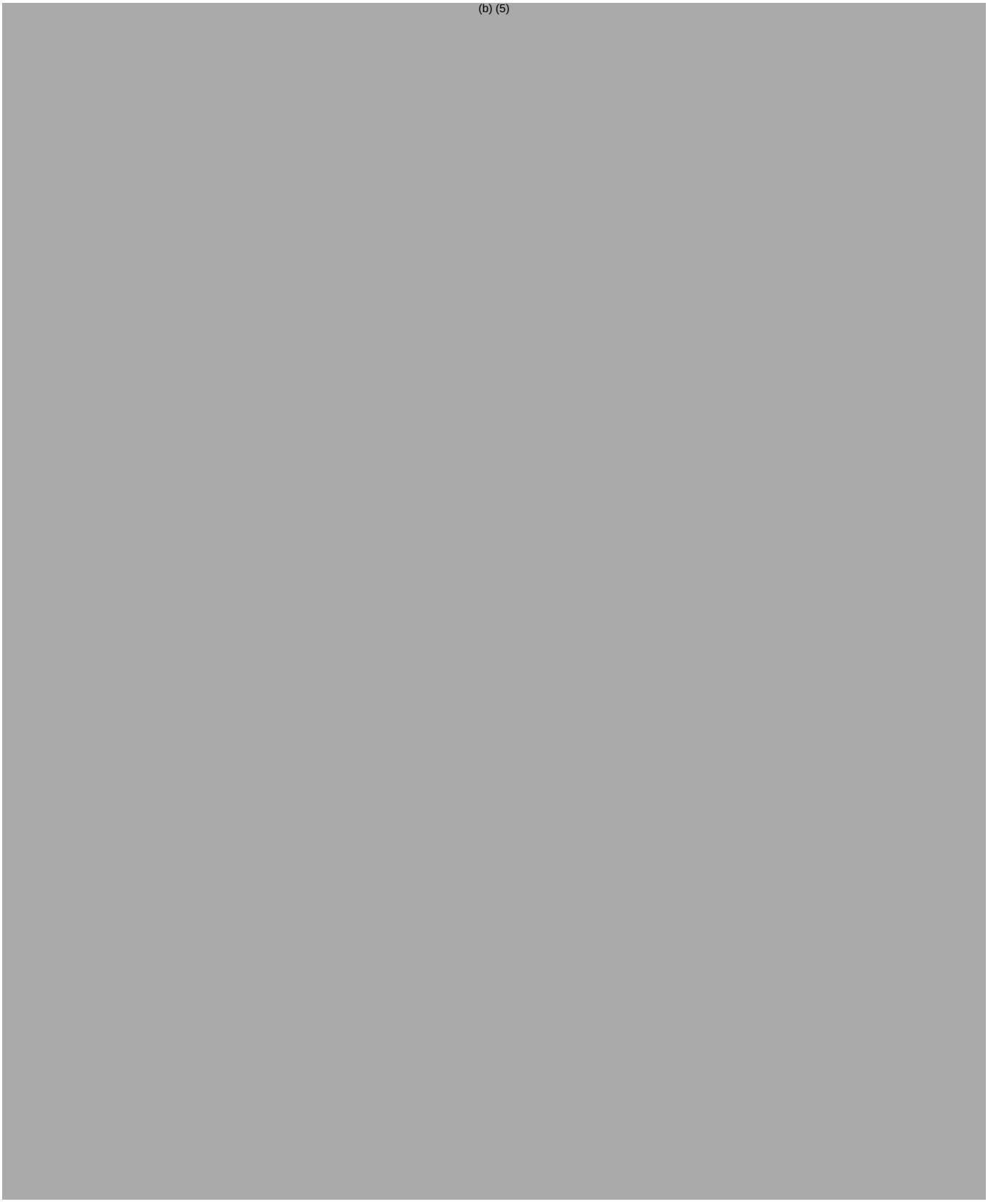

MPPRC – Acetaminophen and Pregnancy

October 3, 2018

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Key Words: acetaminophen, pregnancy, pain, observational study, animal study

Attendance

Council Members:

Jacqueline Corrigan-Curay, OMP
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/s/

JANICE ADAMS
12/10/2018